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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/771,382	PEAK ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,49-52,54,55 and 57-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *33,34 and 49-52* is/are allowed.

6)☒ Claim(s) *54,55 and 57-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed December 31, 2007 has been entered. Claim 57 has been amended. Claims 1-32, 35-48, 53 and 56 have been canceled. Claims 60-61 have been added. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). ***Misnumbered claims 60-61 have been renumbered as claims 59 and 60*** pursuant to 37 CFR 1.126. Claims 33-34, 49-52, 54-55 and 57-60 are under examination.

Rejection Withdrawn

2. In view of Applicant's amendment and response the rejection under 35 U.S.C. 112 first paragraph (new matter), pages 8-10, paragraph 4 of the Final Office action have been withdrawn.

Rejections Maintained

3. The rejection under 35 U.S.C. 112, first paragraph (enablement) is maintained for claims 54-55 and 57-60 for the reasons set forth on pages 2-8, paragraph 3 of the Final Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated proteins as set forth in SEQ ID NOs: 23 and 35 and compositions comprising the isolated proteins, does not reasonably provide enablement for proteins that are variants of SEQ ID NOs: 23 or 35 or compositions comprising these proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification broadly discloses a genus of polypeptides that comprises SEQ ID NO:23 and SEQ ID NO:35. The instant specification teaches that SEQ ID NO: 23 is the amino acid sequence of a PMC 21 NhhA deletion mutant polypeptide (page 8 and Example 4). The instant specification teaches that SEQ ID NO: 35 is the amino acid sequence of a predicted mature protein described in Example 4 (page 10 and Example 4). The instant specification teaches that recombinant DNA-based production of the polypeptides of the invention can be accomplished by the deletion of one or a few amino acids of the (conserved) C1, C2, C3, C4 and/or C5 or (variable) V1, V2, V3 and/or V4 regions of the consensus polypeptide (SEQ ID NO:11) (page 13). The specification teaches that SEQ ID NO:11 comprises constant regions of NhhA polypeptide designated as C1-C5 and non-conserved regions designated as V1-V-4 (page 3). The instant specification teaches that V1-V4 are non-conserved amino acids of a variable region (page 3). Therefore, the non-conserved regions of SEQ ID NO:11 can comprise any amino acid. Thus, the claimed polypeptide as set forth in SEQ ID NO:11 as well as variants of SEQ ID NOs. 23 and 35 can include any substitution or change of amino acids throughout regions V1-V4 of the polypeptide sequence. Therefore, SEQ ID No: 11 and variant or fragments of SEQ ID NOs: 23 and 35 can

correspond to mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth are being claimed. There is no guidance provided as to which amino acids can be substituted, inserted or deleted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation. There is no guidance as to what amino acids may not be changed without causing a detrimental effect to the polypeptide being claimed. The claims broadly teach polypeptides, which include substitutions and/or deletions, therefore any polypeptide is being claimed, and no specific location for the deletion, substitution or any combination thereof is recited. Thus, the resulting polypeptide could result in a polypeptide not taught nor enabled by the specification.

The claims of the instant application are not only drawn to isolated proteins but are also drawn to isolated proteins that have at least 80% or at least 90% identity to SEQ ID NOs. 23 and 35. Thus, the claimed isolated proteins include variants as well as fragments of SEQ ID NOs 23 and 35. There is no guidance provided in the specification as how one would begin to choose " variants or fragments" of SEQ ID NOs: 23 or 35. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

the general tolerance to modification and extent of such tolerance;

- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984*", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into

the interior or the insertion into a helical region of a Praline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186*" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "*Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Therefore, the specification fails to provide guidance regarding how to make and use polypeptides that fall within the broadly claimed genus of SEQ ID NO:11 that retain the claimed activity as well as how to make and use variants or fragments of SEQ ID NOs: 23 and 35.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting polypeptides that fall within the broadly claimed genus of variants or fragments of SEQ ID NOs: 23 and 35 having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are fall within the broadly claimed genus variants or fragments of SEQ ID NOs: 23 and 35 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Applicant's Arguments

Applicant urges that the claims 60 and 61 (renumbered as claims 59 and 60) are fully enabled by the specification. Applicant refers to Table 2 of the specification and urges that a person of skill in the art could replace any of the V regions of SEQ ID NOs: 23-35 with an appropriate conservative substitution. Applicant urges that in view of the correlation between structure and function discussion, *conservative substitutions of one of more amino acids of about 40 amino acids are highly unlikely to significantly adversely affect the immune response to epitopes in about 460 amino acids of the rest of the protein variant.* Applicant urges that a *deletion of one or more amino acids of the about 40 amino acids in the variable region is also highly unlikely to significantly adversely affect the immune response to about 460 amino acids of the rest of the protein.* Applicant urges that Example 10, the deletion of about 80 amino acids from the full length NhhA that contains V1 and V2 did not adversely affect the immune responses to the rest of the sequence in SEQ ID NO:23 or 35 which comprises mainly the C4 and C5 regions. Applicant urges that a deletion mutant elicited an immune response in an animal against the full length PMC21 NHHA polypeptide against the N. meningitidis containing the full length NHHA polypeptide. Applicant urges that by referring to the sequence alignment disclosed in Figure 1, a person of ordinary skill in the art could decide which V region amino acids tend to be more or less conserved between *N. meningitidis* strains, thereby providing further guidance as to which amino acids should be deleted or be substituted with what order to better preserve the overall structure of the protein and have less effect on the immune response to the conserved regions.

and use protein variants of SEQ ID NOs. 23 and 35 and is therefore uncertain of their biological function.

Applicant has not shown which amino acids within the amino acid sequence can be changed and the protein variant retains the same biological function as the parent proteins (amino acid sequence as set forth in SEQ ID NOs. 23 and 35). .Applicant has not given a structure for any of the claimed variants of SEQ ID NO:23 or 35 as recited in claims 59-60,for example.. It should be noted that above cited art references (Thomas E. Creighton and Nosoh, Y. et al) teach that changes in the structure of the amino acid sequence affect the function of any given protein. This also evidenced by Bowie et al (*Science, 1990, 257:1306-1310)* teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. Further, Greenspan et al. (*Nature Biotechnology 17: 936-937, 1999),* disclose defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2).

Based on the teachings of the prior art references, Applicant is not enabled for variants of SEQ ID Nos. 23 and 35 (amino acid sequences that comprises at least one

conservative amino acid substitution in a variable region of SEQ ID NO: 23 or SEQ ID No:35 or a variant comprising at least one deletion of the non-conserved amino acid in a variable region of SEQ ID NO:23 or SEQ ID NO:35) because Applicant has not made a correlation between the structure and function of these claimed variants. It should be noted that claims 59 and 60 *do not recite any particular function.*

To address Applicant's comment regarding example 10, this example merely discloses immunogenicity of purified NhhA deletion mutant polypeptides. In order to satisfy the written description guidelines Applicant must establish a correlation between structure and *specific* function. Applicant has not adequately describe this relationships since there appear to be uncertain as to whether the claimed protein variants have the recited function of eliciting an immune response since there is uncertain as to which epitopes (within the variable region) the amino acid sequences as set forth in SEQ ID NO:23 and 35 have in common with the genus of protein variants encompassed by the claimed invention.

The Examiner disagrees with Applicant assertion that the instant specification shows support for claims 59 and 60. Applicant has not enabled a structure for *any variant* of SEQ ID NO:23 or 35 which comprises all conserved regions of SEQ ID Nos. 23 or 35 and has at least one conserved amino acid substitution or at least one deletion in a variable region of SEQ ID NO:23 or 35. As stated above, Applicant has not shown which amino acids can be changed to arrive at proteins that fall within the scope of the invention. Applicant has not correlated a structure of the claimed variants with any function since claims 59 and 60 do not recite any functional language. Given the

lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a directed immune response, the specification, as filed, is not enabled for the full breath of the claimed invention.

To address Applicant's comments regarding page 14, this page simply refers to the definition of "variants".

To address Figure 1 of the instant specification, the figure discloses the alignments of NhhA polypeptide amino acid sequences from ten *N. meningitides* stains.

To address Table 2 of the instant specification, this table merely discloses conserved amino acid substitutions.

Under the enablement description requirement, Applicant is required to show how to make and use the claimed invention not how to "find" protein variants that fall within the scope of the claimed invention. Thus, Applicant has failed to teach how to make and use the claimed invention. Applicant has not met their burden under 35 U.S.C. 112, first paragraph, scope of enablement.

In view of all of the above, this rejection is maintained.

4. The rejection under 35 U.S.C. 112, first paragraph (written description) is maintained for 54, 55 and 57-60 for the reasons set forth on pages 10-13, paragraph 5 of the Final Office Action.

The rejection is reiterated below:

The claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a written description rejection.*
The specification broadly describes as a part of it's invention, isolated protein variants of SEQ ID NO: 23 or 35 comprising at least one conservative amino acid substitution in a variable region of SEQ OD NO:23 or 35 as well as isolated proteins comprising at least one deletion of a non-conserved amino acid in a variable region of SEQ ID No:23 or 35.

The specification teaches proteins of the invention may therefore have one or more deletions of non-conserved amino acids compared to a corresponding wild-type NhhA polypeptide (page 3).

The instant specification lacks written description for the claimed invention.

Therefore, claimed invention fails to meet the written description provision of 35 U.S.C. 112, first, paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, the instant specification does not provide written description for the full breadth of the claim. Thus the broadly claimed invention does not meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicants Arguments:

Applicant urges that they have discovered that NhhA, a surface antigen has regions that are variable, i.e. V1-V4 and regions that are conserved, i.e. C1-C5, among

different strains of N. meningitidis. Applicant urges that the variable region may contribute to strain-specific immune responses. Applicant urges that that they have produced modified NhhA polypeptides that contain one or more conserved regions and deletion or substitution of one or more non-conserved amino acids in the variable regions to elicit an immune response primarily against conserved epitopes in the conserved region. Applicant refers to Examples 4 and 10 of the instant specification.

Applicant urges that variable regions V3, V4 and a few amino acids in V1 in SEQ ID NOs.23 and 35 constitute only about 40 amino acids out of the approximately 500 amino acids of the sequence. Applicant urges that proteins variants would differ by about 40 amino acids (about 460 out of about 500 amino acids). Applicant urges that the protein variants of claims 59 and 60 *may share common immunogenic epitopes* with those of SEQ ID NOs.23 and 35. Applicant urges that proteins of claims 59 and 60, like SEQ ID NO. 23 or 35 shown in example 10 may elicit an immune response to the full length NhhA protein and thus the N. meningitidis containing the full length NhhA polypeptide. Applicant urges that changes in the variable regions of SEQ ID Nos.23 or 35 *would very unlikely abolish the immune responses to epitopes* in the sequence containing the unchanged 460 amino acids.

Applicant urges that claims 59 and 60 are fully supported by the specification. Applicant urges that one of skill in the would readily discern that Applicants were in possession of the invention at the time of filing. Applicant urges that *ipsis verbis* recitation in the specification is not required. Applicant urges that they describe variants of the modified NhhA polypeptide and how to make them. Applicant points to page 14,

Example 4, Figure 1 and Table 2 of the specification. Applicant urges that the written description requirement does not require the Applicant to provide "longhand" recitation of multiple examples of variant sequences when directly and unambiguously derivable from the sequence information provided by the written description as a whole.

Examiner's Response to Applicant's Arguments:

It is the Examiner's position that claims 54-55 and 57-60 do not comply with 35 U.S.C. 112, first paragraph, written description. Applicant has *not* shown that they are in possession of protein variants comprising at least one conservative amino acid substitution in a variable region of SEQ ID NO:23 or 35 or isolated proteins comprising at least one deletion of a non-conserved amino acid in a variable region of SEQ ID No:23 or 35.

Applicant *has not* made a correlation between structure and function. Applicant has stated on the record (in the October 31, 2007 response) that the claimed protein variants "may *share common immunogenic epitopes* with the proteins as set forth in SEQ ID NOs.23 and 35". Applicant has also stated in the October 31, 2007 response that "changes in the variable regions of SEQ ID Nos.23 or 35 *would very unlikely abolish the immune responses to epitopes* in the sequence containing the unchanged 460 amino acids". The above statements made on the record by Applicant indicate that Applicant is uncertain about the function of the claimed genus of proteins that are variants of SEQ ID Nos. 23 or 35. Thus, the skilled artisan would reasonably conclude that Applicants were not in possession of a representative number of protein variants of

SEQ ID NOs. 23 and 35 at the time of filing and therefore fail to satisfy the written description requirement.

Further, Applicant has not shown which amino acids within the amino acid sequence can be changed and the protein variants the biological function of the parent sequences (SEQ ID No: 23 and 35). Applicant has not given a structure for any of the claimed variants of SEQ ID NO:23 or 35. It should be noted that above cited art references (Thomas E. Creighton and Nosoh, Y. et al) teach that changes in the structure of the amino acid sequence affect the function of any given protein. This is also evidenced by Bowie et al (*Science, 1990, 257:1306-1310)* teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. Further, Greenspan et al. (*Nature Biotechnology 17: 936-937, 1999),* disclose defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2).

Based on the teachings of the prior art references, Applicant has not provided adequate written description for variants of SEQ ID Nos. 23 and 35 (amino acid sequences that comprises at least one conservative amino acid substitution in a

variable region of SEQ ID NO: 23 or SEQ ID No:35 or a variant comprising at least one deletion of the non-conserved amino acid in a variable region of SEQ ID NO:23 or SEQ ID NO:35) because Applicant has not made a correlation between the structure and function of these claimed variants. It should be noted that claims 60 and 61 *do not recite any particular function*.

To address Applicant's comments regarding example 4 of the instant specification, this example merely discloses NhhA mutant construction using convenient restriction site. This example discusses how the amino acid sequences as set forth in SEQ ID NO:23 and 35 were produced. This example fails to show how variants of SEQ ID NOs: 23 and 35 are produced.

To address Applicant's comment regarding example 10, this example merely discloses immunogenicity of purified NhhA deletion mutant polypeptides. In order to satisfy the written description guidelines Applicant must establish a correlation between structure and *specific* function. Applicant has not adequately describe this relationships since there appear to be uncertain as to whether the claimed protein variants have the recited function of eliciting an immune response since there is uncertain as to which epitopes (within the variable region) the amino acid sequences as set forth in SEQ ID NO:23 and 35 have in common with the genus of protein variants encompassed by the claimed invention.

The Examiner disagrees with Applicant's assertion that the instant specification shows support for claims 59 and 60. Applicant has not provided written description for

structures of *any variant* of SEQ ID NO:23 or 35 which comprises all conserved regions of SEQ ID Nos. 23 or 35 and has at least one conserved amino acid substitution or at least one deletion in a variable region of SEQ ID NO:23 or 35. As stated above, Applicant has not shown which amino acids can be changed to arrive at proteins that fall within the scope of the invention. Applicant has not correlated a structure of the claimed variants with any function since claims 59 and 60 do not recite any functional language. Given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a directed immune response, the specification, as filed, the instant invention has failed to satisfy the requirement under written description.

To address Applicant's comments regarding page 14, this page simply refers to the definition of "variants".

To address Applicant's comment regarding example 4 the instant specification, this example merely discloses NhhA mutant construction using convenient restriction site. This example discusses how the amino acid sequences as set forth in SEQ ID NO:23 and 35 were produced. This example fails to show how variants of SEQ ID NOs: 23 and 35 are produced.

To address Figure 1 of the instant specification, the figure discloses the alignments of NhhA polypeptide amino acid sequences from ten *N. meningitides* stains.

To address Table 2 of the instant specification, this table merely discloses conserved amino acid substitutions.

Applicant urges that conservative substitutions or deletion of the one or more amino acids can be achieved by methods known in the art such as site directed mutagenesis or other methods taught in the specification. Applicant urges that the procedures such as disclosed in example 10 of the specification to confirm that the protein variant elicits an immune response against the full length mature NhhA and thus the N. meningitidis is routine in the art and is not undue experimentation.

Examiner's Response to Applicant's Arguments

It is the Examiner's position that claims 54-55 and 57-60 do not comply with 35 U.S.C. 112, first paragraph. It should be noted that the SEQ ID Nos, examined in the invention are SEQ ID NOs. 23 and 35 and not SEQ ID Nos. 23-35. Applicant has shown how to make and use SEQ ID Nos: 23 and 35 but has not shown how to make and use the claimed protein variants of the polypeptide as set forth in SEQ ID Nos:23 and 35. Applicant *has not* made a correlation between structure and function.

Applicant has stated on the record (in the October 31, 2007 response) that the claimed protein variants "may *share common immunogenic epitopes* with the proteins as set forth in SEQ ID NOs.23 and 35". Applicant has also stated in the October 31, 2007 response that "changes in the variable regions of SEQ ID Nos.23 or 35 *would very unlikely abolish the immune responses to epitopes* in the sequence containing the unchanged 460 amino acids". The above statements made on the record by Applicant indicate that Applicant is uncertain about the function of the claimed genus of proteins that are variants of SEQ ID Nos. 23 or 35. Thus, Applicant has not shown how to make

To address Applicant's comment regarding that they not be required to disclose *ipsis verbis* recitation or provide "longhand" recitation of multiple examples of variant sequences when directly and unambiguously derivable from the sequence information provided by the written description as a whole, the Examiner agrees with this assertion. However, Applicant is required to provide: a) defined structure, b) a *specific* function, c) a correlation between the two and d) a representative number of species within the claimed genus of peptides. Providing these elements, shows that Applicants are in possession of the claimed genus of protein variants. Applicant has failed to provide these elements. Thus, Applicant has not met their burden under 35 U.S.C. 112, first paragraph, written description.

In view of all of the above, this rejection is maintained.

Status of Claims

5. Claims 33-34 and 49-52 appear to be free of the cited prior art and are allowable.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vanessa L. Ford
Biotechnology Patent Examiner
January 25, 2008

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